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A microwave-assisted solvent- and catalyst-free synthesis of aminomethylene bisphosphonates

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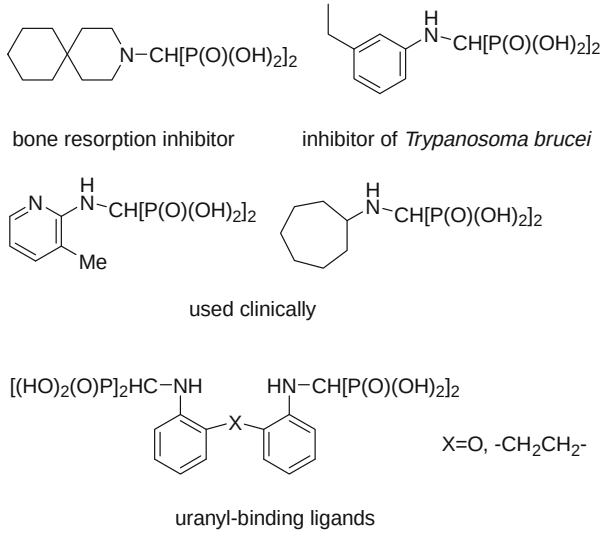
ABSTRACT

A convenient preparative approach for the synthesis of aminomethylene bisphosphonates is developed which involves treatment of amines with triethyl orthoformate and diethyl phosphite under microwave irradiation.

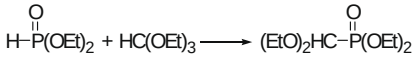
Phosphonic acids are of growing importance in understanding and modulating biological processes.[1] The synthesis of α-substituted phosphoryl derivatives (phosphonic and phosphinic acids) has attracted significant attention due to their biological activities with broad applications as enzyme inhibitors, antimetabolites, and antibiotics.[2] Among α-functionalized phosphonic acids, α-aminoalkylphosphonic derivatives have biological activities such as anti-bacterial,[2] herbicidal,[3] and fungicidal.[4] Aminoalkylphosphonic acids, the phosphonic acid analogues of 2- or α-amino carboxylic acids, are an important class of compounds that exhibit a variety of interesting and useful properties.

In contrast to the widely studied aminophosphonic acid derivatives,[5–8] relatively few papers describe the chemistry of aminomethylene bisphosphonates. Aminomethylene bisphosphonates have been used as powerful inhibitors of the enzyme farnesyl pyrophosphate synthase (FPPS).[9] They display therapeutic properties for conditions such as osteoporosis, rheumatoid arthritis, and cancer (Scheme 1).[10] In addition to these, these compounds possess interesting activities against many parasites including trypanosoma.[11] Besides their biological importance, aminomethylene bisphosphonates are also known for their metal-chelating ability. Recently, the uranyl (UO_2^{2+})-binding properties of these compounds, showing excellent association constants, were reported.[12]

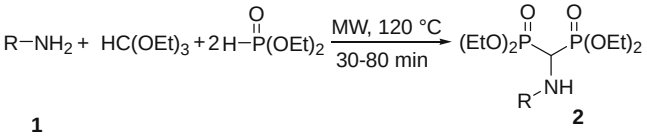
Synthetic routes to aminomethylene bisphosphonates involve prolonged heating in acid-catalyzed reactions of nitriles with phosphites,[13] Mannich-type reaction of amines with triethyl orthoformate and phosphites under nitrogen,[14] phosphorylation of formamides,[15] and Beckmann rearrangement of oximes in the presence of $POCl_3$ followed by treatment with trialkyl phosphites.[16] Recently, a new preparation of aminomethylene bisphosphonates was reported involving the N–H insertion reaction of amines with diphosphonodiazomethane carbene in the presence



Scheme 1. Examples of aminomethylene bisphosphonates used in pharmacy and metal separation.



Scheme 2. Reaction of diethyl phosphite with triethyl orthoformate.



Scheme 3. Reaction of amines with triethyl orthoformate and diethyl phosphite.

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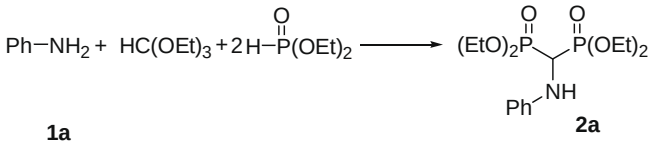
Table 1
One-pot reaction of aniline with triethyl orthoformate and diethyl phosphite under various reaction conditions



1a **2a**

Entry	Reaction conditions[a]	Reaction temperature (°C)	Reaction time (min)	Yield[b] (%) **2a**
1	A	70	48 (h)	11
2	A	120	48 (h)	15
3	B	80	30	25
4	B	100	30	45
5	B	120	30	75
6	B	140	30	75
7	B	120	40	75

[a] A = thermal heating, B = microwave assisted.
[b] Isolated yield.

of rhodium complexes.[12] However, these methods have associated problems, including harsh reaction conditions, long-reaction times and side reactions. On the other hand, the key step in the one-pot synthesis of aminomethylene bisphosphonates is nucleophilic addition of an amine to triethyl orthoformate followed by addition of a phosphite to the resulting imine. Therefore, the formation of diethoxymethyl phosphonates frequently accompanies the formation of aminomethylene bisphosphonates (Scheme 2).[17]

The application of microwave energy to accelerate organic reactions is of increasing interest and offers several advantages over conventional techniques.[18] Syntheses which normally require long periods can be achieved conveniently and very rapidly in a microwave reactor. As part of our efforts to introduce novel methods for the synthesis of organophosphorus compounds,[19] herein we report a new method for the synthesis of aminomethylene bisphosphonates. We have found that microwave-assisted one-pot reactions of amines with triethyl orthoformate and diethyl phosphite give aminomethylene bisphosphonates in good yields (Scheme 3).

Thus, the one-pot reaction of aniline, chosen as a model amine, with triethyl orthoformate and diethyl phosphite was studied under various reaction conditions and the progress of the reaction was monitored by TLC (Table 1). Treatment of **1a** with a mixture of triethyl orthoformate and diethyl phosphite gave the corresponding aminomethylene bisphosphonate **2a** in 11% yield after 48 h at 70 °C (entry 1). When the reaction temperature was raised from 70 °C to 120 °C, the yield of **2a** increased to 15% (entry 2). We found that using a microwave reactor led to acceleration of the reaction rate and an increase in the yield of **2a** (entries 3–7). We obtained the best results on heating at 120 °C for 30 min (entry 5). The yield of the reaction did not change on further increasing the microwave reactor temperature and reaction time (entries 6 and 7).

This process was applied successfully to other amines as summarized in Table 2. Substituted anilines reacted with triethyl orthoformate and diethyl phosphite under microwave irradiation to afford the desired products **2b–i** in moderate to good yields. 1-Naphthylamine also reacted with triethyl orthoformate and diethyl phosphite to give compound **2j** in 55% yield. Reaction of aliphatic amine **1k** and 3-aminopyridine **1l** with triethyl orthoformate and diethyl phosphite gave unidentified mixed products. Reaction of 4-aminodiphenylamine **1m** (with two different amine groups) gave compound **2m** in 85% yield as the only product.

In summary, a series of aminomethylene bisphosphonates have been synthesized via reactions of amines with diethyl phosphite and triethyl orthoformate. The simple work-up, mild reaction conditions, good yields, and clean reactions with no tar formation make this method an attractive and novel contribution to present methodologies.[20]

Table 2
Synthesis of various aminomethylene bisphosphonates under microwave irradiation

Amine **1** R	Product	Reaction time (min)	Yield[a] (%) **2**
C_6H_5–	**2a**	30	75
p-ClC_6H_4–	**2b**	30	70
p-MeC_6H_4–	**2c**	30	80
p-BrC_6H_4–	**2d**	30	70
p-$MeOC_6H_4$–	**2e**	30	82
m-$O_2NC_6H_4$–	**2f**	50	56
m-EtC_6H_4–	**2g**	30	81
o-EtC_6H_4–	**2h**	30	76
4-Cl,2-$O_2NC_6H_3$–	**2i**	80	75
1-Naphthyl	**2j**	60	55
$PhCH_2$–	**2k**	60	—[b]
3-Pyridyl	**2l**	60	—[b]
4-$PhNHC_6H_4$–	**2m**	60	85

[a] Isolated yield.
[b] Unidentified mixture of products.

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20. Diethyl phosphite (15 mmol) was added to a mixture of amine (5 mmol) and triethyl orthoformate (5 mmol) and the solution was stirred for 30–80 min at 120 °C at ambient pressure in a microwave reactor (a Milestone, Micro SYNTH Microwave Labstation for Synthesis, microwave reactor was used for all experiments). The resulting mixture was subjected to column chromatography on silica gel with EtOAc/*n*-hexane (9:1) and evaporation of the solvent under reduced pressure gave pure products in 55–85% yields. All products gave satisfactory spectral data in accord with the assigned structures and literature reports (compounds **2a**, **2e**, **2f**, and **2g**).[11,12] Analytical and spectral data for compounds **2**: *Compound* **2b**: white solid, mp: 137–138 °C; ^{1}H NMR (CD_3SOCD_3—250 MHz), δ: 1.05–1.23 (m, 12H), 3.91–4.18 (m, 8H), 4.53 (dt, 1H, J_{HP} = 22.8 Hz, J = 10.5 Hz), 5.97 (d, 1H, NH, J = 10.5 Hz), 6.90 (d, 2H, J = 8.8 Hz), 7.06 (2H, J = 8.8 Hz). ^{31}P NMR (CD_3SOCD_3—101.25 MHz), δ: 18.36. ^{13}C NMR (CD_3SOCD_3—62.9 MHz), δ: 16.6 (d, J_{PC} = 2.5 Hz), 48.8 (t, J_{PC} = 145.2 Hz), 62.7–63.2 (m), 114.9, 120.6, 128.6, 146.5 (t, J_{PC} = 3.7 Hz). Anal. Calcd for $C_{15}H_{26}NO_6P_2Cl$: C, 43.57; H, 6.29; N, 3.39. Found: C, 43.63; H, 6.20; N, 3.45. *Compound* **2c**: white solid, mp: 70–71 °C; ^{1}H NMR (CD_3SOCD_3—250 MHz), δ: 1.05–1.25 (m, 12H), 2.13 (s, 3H), 3.90–4.13 (m, 8H), 4.42 (dt, 1H, J_{HP} = 22.8 Hz, J = 10.5 Hz), 5.42 (d, 1H, NH, J = 10.5 Hz), 6.76 (d, 2H, J = 8.2 Hz), 6.87 (2H, J = 8 Hz). ^{31}P NMR (CD_3SOCD_3—101.25 MHz), δ: 18.69. ^{13}C NMR (CD_3SOCD_3—62.9 MHz), δ: 16.5 (d, J_{PC} = 2.5 Hz), 20.4, 49.1 (t, J_{PC} = 145.9 Hz), 62.8–63.4 (m), 113.6, 126.1, 129.5, 144.9 (t, J_{PC} = 4.4 Hz). Anal. Calcd for $C_{16}H_{29}NO_6P_2$: C, 48.84; H, 7.43; N, 3.56. Found: C, 48.61; H, 7.55; N, 3.50. *Compound* **2d**: white solid, mp: 139–140 °C; ^{1}H NMR (CD_3SOCD_3—250 MHz), δ: 1.03–1.30 (m, 12H), 3.89–4.18 (m, 8H), 4.53 (dt, 1H, J_{HP} = 22.8 Hz, J = 10.5 Hz), 6.00 (d, 1H, NH, J = 10.5 Hz), 6.86 (d, 2H, J = 8.5 Hz), 7.17 (2H, J = 8.5 Hz). ^{31}P NMR (CD_3SOCD_3—101.25 MHz), δ: 18.31. ^{13}C NMR (CD_3SOCD_3—62.9 MHz), δ: 16.1 (d, J_{PC} = 1.8 Hz), 48.7 (t, J_{PC} = 145.2 Hz), 62.7–63.2 (m), 108.0, 115.5, 131.4, 146.9 (t, J_{PC} = 3.7 Hz). Anal. Calcd for $C_{15}H_{26}NO_6P_2Br$: C, 39.38; H, 5.73; N, 3.06. Found: C, 39.15; H, 5.70; N, 2.93. *Compound* **2h**: colorless oil; ^{1}H NMR (CD_3SOCD_3–TMS, 250 MHz), δ: 1.02–1.25 (m, 15H), 2.40 (q, 2H, J = 7.5 Hz), 3.90–4.18 (m, 8H), 4.71 (dt, 1H, J_{HP} = 22 Hz, J = 10.25 Hz), 6.64 (t, 1H, J = 7.5 Hz), 7.85–7.08 (m, 3H). ^{31}P NMR (CD_3SOCD_3–TMS, 101.25 MHz), δ: 18.70. ^{13}C NMR (CD_3SOCD_3–TMS, 62.9 MHz), δ: 13.5, 16.4–16.6 (m), 23.8, 49.1 (t, J_{PC} = 144.6 Hz), 62.6–63.2 (m), 112.0, 118.3, 127.1, 128.0, 128.5, 143.8 (t, J_{PC} = 4.4 Hz). Anal. Calcd for $C_{17}H_{31}NO_6P_2$: C, 50.10; H, 7.67; N, 3.44. Found: C, 49.95; H, 7.55; N, 3.52. *Compound* **2i**: colorless oil; ^{1}H NMR (CD_3SOCD_3—250 MHz), δ: 1.03–1.24 (m, 12H), 3.98–4.17 (m, 8H), 5.36 (dt, 1H, J_{HP} = 21.75 Hz, J = 10.5 Hz), 7.53 (d, 1H, J = 9.25 Hz), 7.56 (dd, 1H, J = 9.25 Hz, J = 2.5 Hz), 8.08 (d, 1H, J = 2.5 Hz), 8.27 (d, 1H, NH, J = 7.5 Hz). ^{31}P NMR (CD_3SOCD_3—101.25 MHz), δ: 16.75. ^{13}C NMR (CD_3SOCD_3—62.9 MHz), δ: 16.3–16.7 (m), 48.1 (t, J_{PC} = 143.4 Hz), 62.5, 118.5, 120.8, 125.3, 132.6, 136.6, 143.0 (t, J = 5.03 Hz). Anal. Calcd for $C_{15}H_{25}N_2O_8P_2Cl$: C, 39.29; H, 5.50; N, 6.11. Found: C, 39.11; H, 5.67; N, 6.05. *Compound* **2j**: white solid, mp: 63–64 °C; ^{1}H NMR (CD_3SOCD_3–TMS, 250 MHz), δ: 1.01–1.28 (m, 12H), 3.90–4.21 (m, 8H), 4.83 (dt, 1H, J_{HP} = 22.5 Hz, J = 10 Hz), 5.34 (d, 1H, NH, J = 9.5 Hz), 6.98 (d, 1H, J = 7 Hz), 7.17–7.60 (m, 4H), 7.72–7.85 (m, 1H), 7.95–8.09 (m, 1H). ^{31}P NMR (CD_3SOCD_3–TMS, 101.25 MHz), δ: 18.55. ^{13}C NMR (CD_3SOCD_3–TMS, 62.9 MHz), δ: 16.3, 49.1 (t, J_{PC} = 146.5 Hz), 63.5–64.0 (m), 106.3, 118.5, 120.6, 123.4, 125.5, 126.3, 126.7, 128.7, 134.2, 141.5. Anal. Calcd for $C_{19}H_{29}NO_6P_2$: C, 53.13; H, 6.81; N, 3.26. Found: C, 52.95; H, 6.63; N, 3.10. *Compound* **2m**: white solid, mp: 81–82 °C; ^{1}H NMR (CD_3SOCD_3—250 MHz), δ: 1.03–1.25 (m, 12H), 3.92–4.24 (m, 8H), 4.44 (dt, 1H, J_{HP} = 22.5 Hz, J = 10.5 Hz), 5.37 (d, 1H, NH, J = 10.5 Hz), 6.62 (t, 1H, J = 7.5 Hz), 6.77–6.95 (m, 6H,), 7.09 (t, 2H, J = 8.25 Hz), 7.57 (s, NH, 1H). ^{31}P NMR (CD_3SOCD_3—101.25 MHz), δ: 18.77. ^{13}C NMR (CD_3SOCD_3—62.9 MHz), δ: 16.4, 49.6 (t, J_{PC} = 145.9 Hz), 63.3–63.7 (m), 114.5, 114.6, 118.2, 121.5, 129.4, 133.9, 141.9 (t, J_{PC} = 4.3 Hz), 146.0. Anal. Calcd for $C_{21}H_{32}N_2O_6P_2$: C, 53.60; H, 6.86; N, 5.96. Found: C, 53.51; H, 6.74; N, 5.86.